IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

H. Lundbeck A/S
Ottiliavej 9
Valby-Copenhagen
Denmark DK-2500

Plaintiff,

v.

HON. DAVID J. KAPPOS
Under Secretary of Commerce for Intellectual Property and
Director of the United States Patent and Trademark Office
Office of General Counsel,
United States Patent and Trademark Office
Madison Building East, Rm. 10B20
600 Dulany Street, Alexandria, VA 22314

Defendant.

COMPLAINT

Plaintiff, H. Lundbeck A/S ("Lundbeck"), for its complaint against the Honorable David J. Kappos, states as follows:

NATURE OF THE ACTION

1. This is an action by the assignee of United States Patent No. 7,767,683 ("the '683 patent") seeking judgment, pursuant to 35 U.S.C. § 154(b)(4)(A), that the patent term adjustment for the '683 patent be changed from 96 days to 290 days.

2. This action arises under 35 U.S.C. § 154 and the Administrative Procedures Act, 5 U.S.C. §§ 701-706.

salts, pharmaceutical compositions, and methods of treatment. The '683 patent is attached as Exhibit A.

9. Plaintiff Lundbeck is the assignee of the '683 patent.

10. Under Section 154 of Title 35 of the United States Code, the Director of the PTO must grant a patent term adjustment in accordance with the provisions of section 154(b), which states, in pertinent part, that "[t]he Director shall proceed to grant the patent after completion of the Director's determination of a patent term adjustment under the procedures established under this subsection, notwithstanding any appeal taken by the applicant of such determination." 35 U.S.C. § 154(b)(3)(D).

11. In determining patent term adjustment, the Director is required to extend the term of a patent for a period equal to the total number of days attributable to delay by the PTO under 35 U.S.C. §§ 154(b)(l)(A), (B), and (C), as limited by the following: (i) any overlapping periods of PTO delay as specified by 35 U.S.C. § 154(b)(2)(A); (ii) any disclaimer of patent term by the applicant under 35 U.S.C. § 154(b)(2)(B); and (iii) any delay attributable to the applicant under 35 U.S.C. § 154(b)(2)(C).

12. The Director determined that the '683 patent is entitled to 96 days of patent term adjustment pursuant to 35 U.S.C. § 154(b)(3) and issued the '683 patent reflecting that determination.

13. On October 1, 2010, in accordance with 37 C.F.R. 1.705(d), Lundbeck filed an Application for Patent Term Adjustment ("Application for PTA") with the PTO to request correction of the Director's patent term adjustment determination. The Application for PTA is attached as Exhibit B.

20. Section 154(b)(1)(B)(i) of Title 35 excludes from the calculation of B Delay "any time consumed by continued examination of the application." The Director erred in the calculation of patent term adjustment by subtracting from B Delay a period of time that was not "consumed by continued examination of the application." The PTO mailed a Notice of Allowance on March 22, 2010, thereby closing examination of the application on that date. Thus, no continued examination took place during the 135 day period from March 22, 2010 (the mailing date of the Notice of Allowance) until August 3, 2010 (the date the '683 patent issued). Accordingly, 135 days of B Delay should have been included in addition to the 144 days accorded by the Director, for a total B Delay of 279 days.

21. Under 35 U.S.C. § 154(b)(2)(C), the correct number of days of applicant delay is 201 days, corresponding to four periods of delay occurring: (i) from August 14, 2008 to November 13, 2008, for a period of 92 days; (ii) from April 23, 2009 to July 16, 2009, for a period of 85 days; (iii) from May 24, 2010 to May 27, 2010, for a period of 4 days; and (iv) from June 2, 2010 to June 21, 2010, for a period of 20 days. The Director incorrectly calculated a total applicant delay of 260 days.

22. The Director correctly calculated periods of applicant delay as occurring: (i) from August 14, 2008 to November 13, 2008; and (ii) from April 23, 2009 to July 16, 2009.

23. The Director incorrectly calculated periods of applicant delay in three separate instances, as explained in each of the following three paragraphs.

24. A Request for Corrected Filing Receipt was filed on May 24, 2010, subsequent to the mailing of a Notice of Allowance. As part of the request for correction of the filing receipt, a Supplemental Application Data Sheet was submitted containing the changes to be made by the correction. The PTO responded to the filing on May 27, 2010, by issuing a Corrected Filing

mailing address. Although the filing of a paper to change an address is not mentioned in 37 C.F.R. § 1.704(c)(10), such a filing is specifically addressed in the section of MPEP 2732 that clarifies the types of papers filed after allowance that are not considered to be a failure to engage in reasonable efforts to conclude processing or examination of an application under 37 C.F.R. § 1.704(c)(10). According to MPEP 2732, papers filed after allowance that are "**not** considered to be a failure to engage in reasonable efforts to conclude processing or examination of an application [include] ... (4) Change of Address" *Id.* Because the Supplemental Application Data Sheet filed on June 22, 2010 related only to corrections of the practitioner's email address and an inventor's mailing address, an assessment of applicant delay for this filing is inappropriate. Furthermore, there is no indication that this post-allowance filing caused any amount of actual delay in the processing of the application or the issuance of the patent (the patent issued in a mere 43 days after payment of the issue fee, without the PTO mailing any notice in response to the Supplemental Application Data Sheet). An applicant submission that does not cause any delay in the processing or examination of an application cannot be treated by the PTO as a cause of applicant delay. The 43 days of applicant delay assessed by the PTO from June 22, 2010 to August 3, 2010 should be adjusted to 0 days.

27. Section 154(b)(2)(A) of Title 35 provides that "to the extent that periods of delay attributable to grounds specified in paragraph [b](1) overlap, the period of any adjustment . . . shall not exceed the actual number of days the issuance of the patent was delayed." The overlap between the A Delay period and the B Delay period in the prosecution of the '683 patent is 0 days. The Director correctly calculated the overlap between the A Delay period and the B Delay period.

Dated: January 28, 2011

Respectfully Submitted,

Andrew R. Kopsidas, Bar No. 476237
kopsidas@fr.com
FISH & RICHARDSON P.C.
1425 K Street, N.W.
Washington, D.C. 20005
Telephone: 202-783-5070
Facsimile: 202-783-2331

Attorney for Plaintiff
H. Lundbeck A/S

US007767683B2

(12) **United States Patent**
Lopez de Diego et al.

(10) **Patent No.: US 7,767,683 B2**
(45) **Date of Patent: Aug. 3, 2010**

(54) **HYDROGEN SUCCINATE SALTS OF TRANS-4-((1R, 3S)-6-CHLORO-3-PHENYLINDAN-1-YL)-1,2,2-TRIMETHYLPIPERAZINE AND THE USE AS A MEDICAMENT**

(75) Inventors: **Heidi Lopez de Diego**, Naerum (DK); **Ole Nielsen**, Valby (DK); **Lone Munch Ringgard**, Roskilde (DK); **Henrik Svane**, Virum (DK); **Allan Carsten Dahl**, Nyrup (DK); **Mark Howells**, Copenhagen S (DK); **Benny Bang-Andersen**, Copenhagen S (DK); **Lars Ole Lyngso**, Vekso Sj (DK); **Sherry Lynn Collier**, Flemington, NJ (US)

(73) Assignee: **H. Lundbeck A/S**, Valby-Copenhagen (DK)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 96 days.

(21) Appl. No.: **10/568,572**

(22) PCT Filed: **Aug. 18, 2004**

(86) PCT No.: **PCT/DK2004/000545**

§ 371 (c)(1),
(2), (4) Date: **Aug. 14, 2006**

(87) PCT Pub. No.: **WO2005/016900**

PCT Pub. Date: **Feb. 24, 2005**

(65) **Prior Publication Data**

US 2006/0281759 A1 Dec. 14, 2006

Related U.S. Application Data

(60) Provisional application No. 60/496,058, filed on Aug. 18, 2003, provisional application No. 60/520,246, filed on Nov. 14, 2003.

(30) **Foreign Application Priority Data**

Aug. 18, 2003 (DK) 2003 01180
Sep. 11, 2003 (DK) 2003 01305

(51) **Int. Cl.**
A61K 31/495 (2006.01)
C07D 241/04 (2006.01)

(52) **U.S. Cl.** **514/255.03**; 544/403

(58) **Field of Classification Search** ..... None
See application file for complete search history.

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Primary Examiner—Emily Bernhardt
(74) *Attorney, Agent, or Firm*—Stephen G. Kalinchak; Margaret M. Buck

(57) **ABSTRACT**

4-((1R,3S)-6-Chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine hydrogen succinate, pharmaceutical compositions containing the salt and the medical use thereof, including for the treatment of schizophrenia and other psychotic disorders. Also described are methods for the preparation of 4-((1R,3S)-6-Chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine and medical uses thereof.

12 Claims, 3 Drawing Sheets

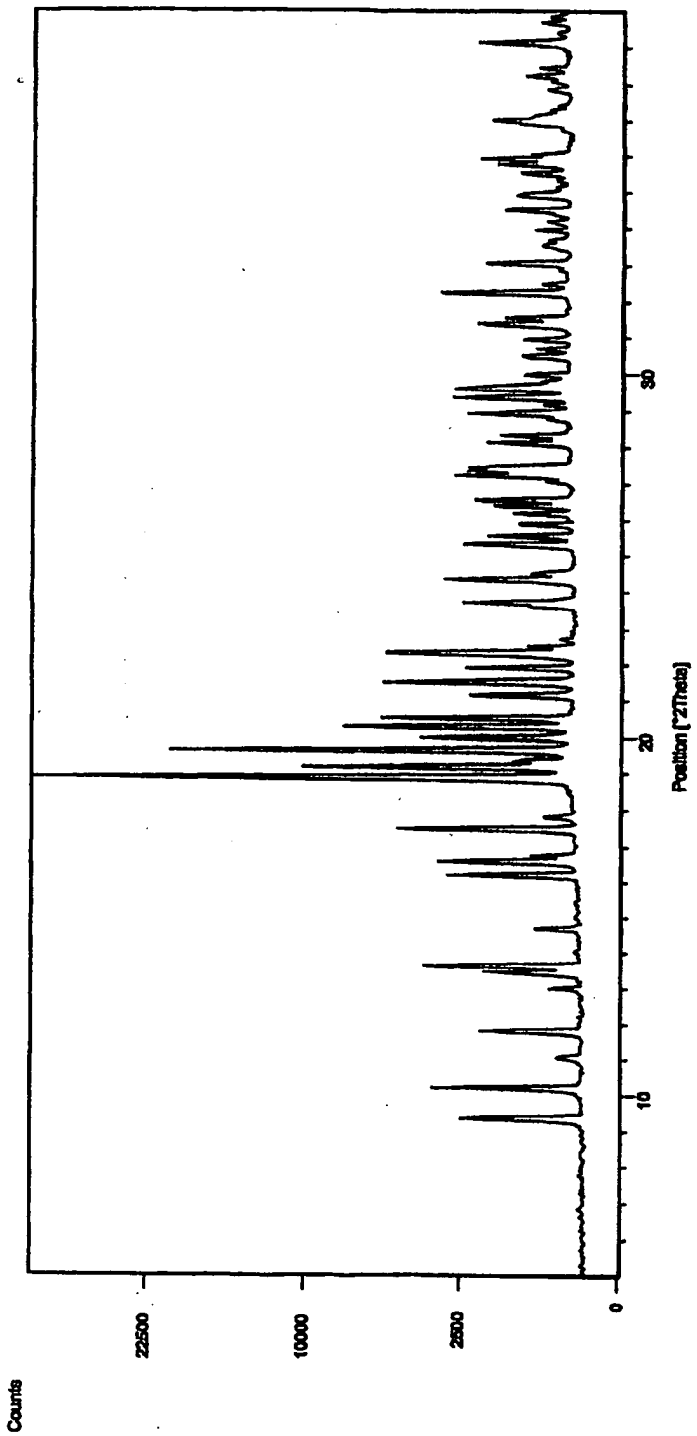


Fig. 1

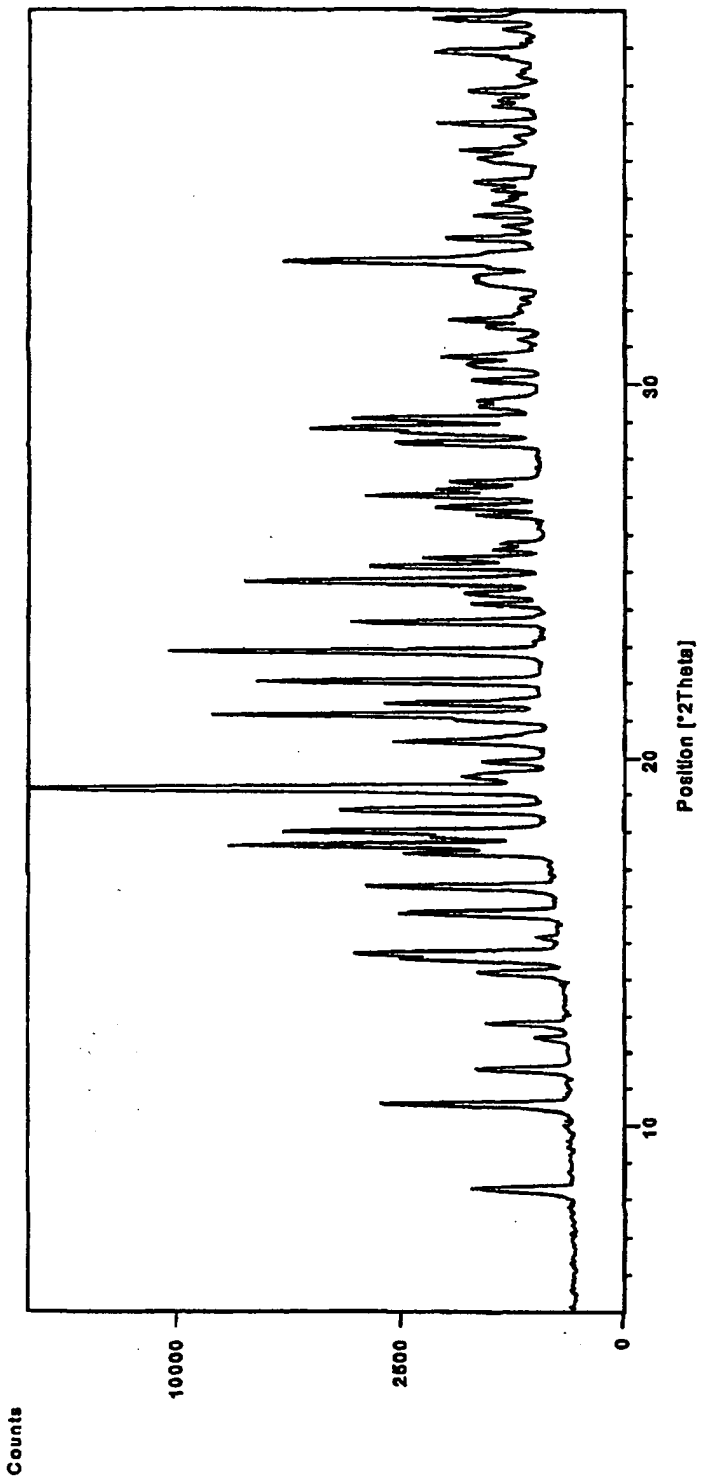


Fig. 3

DETAILED DESCRIPTION OF THE INVENTION

Salts of the Invention

It has now been found that the aqueous solubility of the hydrogen succinate salt and of the hydrogen malonate salt of the compound of formula (I) is considerably larger than the aqueous solubility of the corresponding fumarate salt.

As used herein the term "hydrogen succinate" salt of the compound of formula (I) refers to the 1:1 salt of the compound of formula (I) and succinic acid.

As used herein the term "hydrogen malonate" salt of the compound of formula (I) refers to the 1:1 salt of the compound of formula (I) and malonic acid.

The hydrogen succinate salt was found to be more stable than the fumarate salt and than the hydrogen malonate salt and to be non-hygroscopic.

The hydrogen malonate salt of Compound I was found to have a stability similar to the fumarate salt when exposed to light and more stable when exposed to 60° C./80% relative humidity (RH), but less stable than the fumarate salt at 90° C. 90° C. is however a very stressed condition, and does not necessarily relate to stability at normal conditions. The malonate absorbs gradually up to 1% of water when the relative humidity is raised to 95%, but with no hysterhesis. It is therefore considered as non-hygroscopic, but with good wetting properties, which indicates favourable dissolution properties.

The invention also covers crystalline salts of the invention, including, e.g. anhydrates hydrates, and solvates of the salts of the invention. By the term anhydrate is meant the salts of the invention containing no crystal bound water. By hydrates is meant the salts of the invention containing crystal bound water molecules. Hydrates are usually prepared by formation of the salt in presence of some water. By solvates is meant the salts of the invention containing crystal bound solvent molecules. Solvates are usually prepared by formation of the succinate salt in presence of the solvent. The solvent molecules in a single solvate may be of one or two or more different solvents. A solvate may comprise water as one of two or more organic solvents or be only a non-water solvent.

One embodiment of the invention relates to the 1:1 salt of trans-4-((1R,3S)-6-Chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine, i.e. of the compound of formula (I), and succinic acid in the form of a crystalline anhydrate.

The inventors have discovered 2 crystalline forms of the hydrogen succinate salt of Compound I (named alpha and beta).

Thus, one embodiment relates to a crystalline form of the hydrogen succinate salt of Compound I, which form is named alpha and characterized by one or more of:

(i) an X-Ray powder diffractogram as shown in FIG. 1;

(ii) an X-Ray powder diffractogram pattern as illustrated in Table I obtained using copper $K_{\alpha 1}$ radiation (λ=1.5406 Å) which shows main peaks at the 2θ-angles given;

(iii) having a DSC (Differential Scanning Calorimetry) trace which shows an endotherm with onset 139-141° C.

A further embodiment relates to a crystalline form of the hydrogen succinate salt of Compound I, which form is named beta and characterized by one or more of:

(i) an X-Ray powder diffractogram as shown in FIG. 2;

(ii) an X-Ray powder diffractogram pattern as illustrated in Table I obtained using copper $K_{\alpha 1}$ radiation (λ=1.5406 Å) which shows main peaks at the 2θ-angles given;

(iii) having a DSC trace which shows an endotherm with onset 135-138° C.

A further embodiment relates to a crystalline hydrogen malonate salt of Compound I characterized by one or more of:

(i) an X-Ray powder diffractogram as shown in FIG. 3;

(ii) an X-Ray powder diffractogram pattern as illustrated in Table I obtained using copper $K_{\alpha 1}$ radiation (λ=1.5406 Å) which shows main peaks at the 2θ-angles given.

TABLE 1

Characteristic X-Ray powder diffractograms obtained using copper $K_{\alpha 1}$ radiation (λ = 1.5406 Å) of the crystal forms alpha and beta of the hydrogen succinate salt of Compound I, and of the crystalline hydrogen malonate salt of Compound I. Fig; cf. also FIG. 1, FIG. 2 and FIG. 3 providing a representative XRPD pattern of polymorphic form alpha and beta of the hydrogen succinate salt and of the malonate salt of Compound I, respectively.

Salt	Characteristic reflexes - main peaks (expressed in degree of diffraction angle 2θ)
Succinate, alpha	9.36; 10.23; 11.81; 13.45; 16.21; 16.57; 17.49; 18.89; 19.20; 19.63; 20.01; 20.30; 21.15; 21.53; 21.93; 22.34; 24.37; 25.34; 27.27; 29.65
Succinate, beta	8.1; 10.5; 11.4; 14.0; 14.6; 15.6; 15.7; 16.2; 17.2; 17.5; 17.9; 18.4; 18.9; 19.2; 20.3; 21.0; 21.9; 22.5; 23.3; 26.3
Malonatet	8.3; 10.6; 11.5; 12.8; 14.2; 14.5; 14.7; 15.8; 16.5; 17.4; 17.6; 18.0; 18.6; 19.2; 21.2; 22.0; 22.9; 23.7; 24.7; 28.8

As used herein by expressions like "crystalline form of a specific salt of Compound I characterized by the X-Ray powder diffractogram shown in FIG. (1)" is meant the crystalline form of salt of Compound I in question having an X-ray powder diffractogram substantially similar to FIG. (1), i.e. exhibiting an X-ray powder diffraction pattern substantially as exemplified in that Figure and measured under comparable conditions as described herein or by any comparable method.

Generally, all data herein are understood to be approximate and subject to normal measurement error depending e.g. on the apparatus used and other parameters influencing peak positions and peak intensities.

The invention also relates to a solid hydrogen succinate salt of Compound I which solid salt consist mainly of the alpha form as compared to the total amount of the salt. In one embodiment, the term "mainly" means that the solid hydrogen succinate salt of Compound I consist of at least 75%, such as at least 80%, at least 90%, or at least 95% crystalline alpha form as compared to the total hydrogen succinate salt of Compound I present.

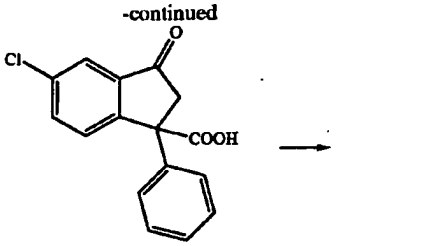
The invention also relates to a solid hydrogen succinate salt of Compound I which solid salt consist mainly of the beta form as compared to the total amount of the salt. In one embodiment, the term "mainly" means that the solid hydrogen succinate salt of Compound I consist of at least 75%, such as at least 80%, at least 90%, or at least 95% crystalline beta form as compared to the total hydrogen succinate salt of Compound I present.

The invention also relates to any mixtures of the crystalline forms of the hydrogen succinate salt of the invention, e.g. a mixture of the alpha and beta crystalline form of the hydrogen succinate salt of Compound I.

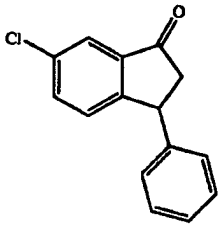
Preparation of the Salts of the Invention

The succinate salt according to the invention may be obtained by treatment of the free base of a compound of formula (I) with succinic acid in an inert solvent followed by precipitation, isolation and optionally recrystallization. If desired, the crystalline salt may thereafter be subjected to

-continued

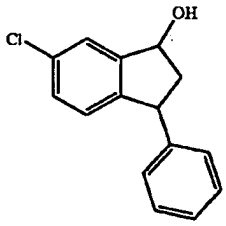


(III)



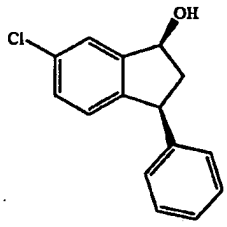
(IV)

The compound of formula (IV) is then reduced, suitably with $NaBH_4$ in a solvent such as an alcohol, e.g. ethanol or iso-propanol, and preferably at a temperature in the range of −30° to +30° C., e.g. below 30° C., below 20° C., below 10° C., or preferably below 5° C., to form a compound of formula (V) with cis configuration:



(V)

The compound of formula (V) is resolved to achieve the desired enantiomer (formula Va), i.e. also with cis configuration ((1S,3S)-6-chloro-3-phenylindan-1-ol):



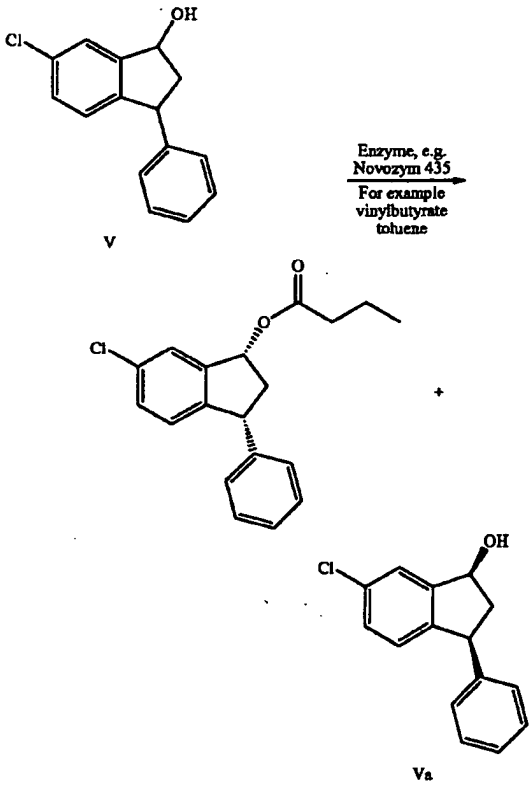
(Va)

The resolution of (V) to (Va) may, e.g., be performed using chiral chromatography, preferably liquid chromatography, suitably on a chiral column of silicagel coated with a chiral polymer, e.g. a modified amylose, preferably amylose tris-(3,5-dimethylphenylcarbamate) coated on silicagel. A suitable solvent is used for the chiral liquid chromatography, such as, e.g. an alcohol, a nitrile, an ether, or an alkane, or mixtures thereof, suitably ethanol, methanol, iso-propanol, acetonitrile, or methyl tert-butyl ether or mixtures thereof, preferably methanol or acetonitrile. The chiral liquid chromatography can be scaled up using suitable technologies, e.g. simulated moving bead technology (SMB).

Alternatively, the compound of formula (V) is resolved to achieve Compound Va by enzymatic resolution. It has been found that enantiomerically pure Compound Va, or acylated derivatives thereof, may be prepared by enzymatic enantioselective acylation of the hydroxyl group in racemic Compound V to obtain Compound Va or an acylated derivative thereof with high optical purity. Alternatively, enantiomerically pure Compound Va may also be obtained by a process comprising converting racemic Compound V to a corresponding ester in the hydroxyl position followed by an enzymatic enantioselective deacylation. Use of enzymatic enantioselective deacylation has been reported for other compounds.

Accordingly, The resolution of Compound V to Compound Va may be performed by selective enzymatic acylation. Selective enzymatic acylation means that the enzymatic acylation is preferentially effective for conversion of one of the cis-enantiomers of the compound of formula Compound V leaving the other cis-enantiomer of Compound V as unconverted in the reaction mixture.

Alternatively, The resolution of Compound V to Compound Va may be performed by selective enzymatic deacylation. Selective enzymatic deacylation means that the enzymatic deacylation is preferentially effective for conversion of one of the esters of compound of formula (V), leaving the other cis-enantiomer of esters of a compound of formula (V) as unconverted in the reaction mixture.



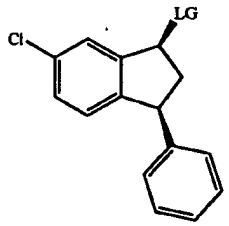
V

Va

(Novozymes A/S); or Lipozyme TL IM (Thermomyces lanuginosus lipase) (Novozymes A/S), preferably in immobilized form.

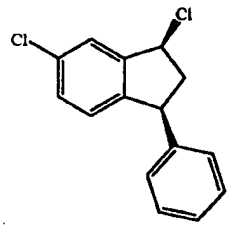
The alcohol group of the cis-alcohol of formula (Va) is converted to a suitable leaving group, such as, e.g., a halogen, e.g. Cl or Br, preferably Cl, or a sulphonate, e.g. mesylate or tosylate, suitably by reaction with an agent, such as thionyl chloride, mesyl chloride or tosyl chloride, in an inert solvent, e.g. an ether, suitably tetrahydrofuran. The resulting compound has formula (VI), where LG is the leaving group:

(VI)



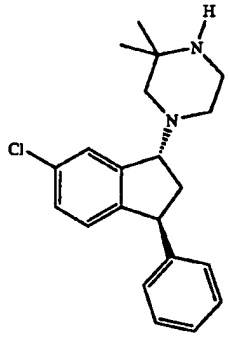
In a preferred embodiment, LG is Cl, i.e. the cis-chloride of formula (VIa):

(VIa)



Compound VI, e.g. with LG as chloro, is then reacted with 2,2-dimethylpiperazine in a suitable solvent, e.g. a ketone such as, e.g., methyl isobutyl ketone or methyl ethyl ketone, preferably methyl isobutyl ketone in presence of a base, such as e.g., potassium carbonate. The resulting compound of formula (VII):

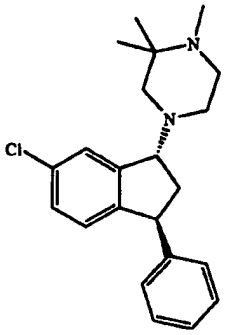
(VII)



is methylated at the secondary amine functionality (suitably by reductive amination using suitable agents, such as, e.g., formaldehyde, paraformaldehyde, trioxane, or diethoxy

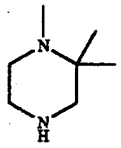
methane (DEM) to obtain the free base of a compound of formula (I).

(I)



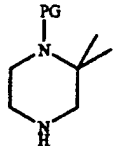
Alternatively, the methyl group may be introduced directly by use of 1,2,2-trimethyl piperazine (Formula VIII below) instead of 2,2-dimethyl piperazine when reacting with Compound VI, e.g. where LG is Cl, thereby shortening the synthesis by one step.

(VIII)

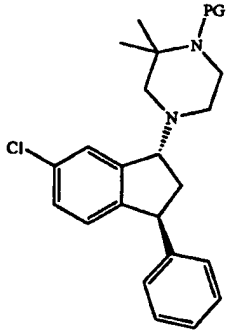


Furthermore, the piperazine part of the molecule may be introduced by reacting Compound VI with a compound of formula (IX) below, where PG is a protecting group such as, but not restricted to, e.g. phenylmethoxycarbonyl (often called Cbz or Z), tert-butyloxycarbonyl (often called BOC), ethoxycarbonyl, or benzyl, thereby obtaining the compound of formula (X) below.

(IX)



(X)



After deprotection of the product to (VII), methylation as discussed above gives the final product, Compound I. Alternatively, the protecting group such as e.g. ethoxycarbonyl may be converted directly to a methyl group using a suitable reducing agent, e.g. lithium aluminium hydride.

During the synthesis some cis diastereoisomer of Compound I (i.e. 4((1S,3S)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine) is formed as an impurity in the final

90%, at least 95%, at least 97%, at least 98%. One embodiment relates to substantially pure Compound VII or a salt thereof.

A further aspect relates to Compound I or a salt thereof, in particular the fumarate, malonate, or succinate salt, obtainable, in particular obtained, by a method of the invention as described herein.

A further aspect relates to Compound VII or a salt thereof, e.g. the fumarate salt, obtainable, in particular obtained, by a method of the invention as described herein.

Pharmaceutical Use

The physical properties of the Compound I salts of the invention indicate that they will be particularly useful as a pharmaceutical.

Accordingly, the present invention further relates to a pharmaceutical composition of the succinate salt, in particular the hydrogen succinate salt as described herein (e.g. the alpha or beta form as described herein), or of the malonate salt, in particular the hydrogen malonate salt, of the compound of formula (I). The invention also relates to the medical use of such salts and compositions, such as for the treatment of a disease in the central nervous system, including psychosis, in particular schizophrenia or other diseases involving psychotic symptoms, such as, e.g., Schizophrenia, Schizophreniform Disorder, Schizoaffective Disorder, Delusional Disorder, Brief Psychotic Disorder, Shared Psychotic Disorder as well other psychotic disorders or diseases that present with psychotic symptoms, e.g. mania in bipolar disorder.

Additionally, the 5-HT_2 antagonistic activity of compound of the invention suggests that the compound may have a relatively low risk of extrapyramidal side effects.

The present invention also relates to use of the succinate or malonate salt of the invention, preferably the hydrogen succinate (e.g. the crystalline form alpha) or hydrogen malonate salt, of the compound of formula (I) for treatment of a disease selected from the group consisting of anxiety disorders, affective disorders including depression, sleep disturbances, migraine, neuroleptic-induced parkinsonism, cocaine abuse, nicotine abuse, alcohol abuse and other abuse disorders.

In a broad aspect, the present invention relates to a method of treating Schizophreniform Disorder, Schizoaffective Disorder, Delusional Disorder, Brief Psychotic Disorder, Shared Psychotic Disorder or mania in bipolar disorder, comprising administering a therapeutically effective amount of the compound trans-4-(6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine or a salt thereof.

As used herein the term "trans-4-(6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine", i.e. without any specific indication of the enantiomer form (e.g. using (+) and (−), or using the R/S-convention, is meant to refer to any enantiomeric form of this compound, i.e. either of the two enantiomers, 4-((1R,3S)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine (I) or 4-((1S,3R)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine or to a mixture of the two, e.g. the racemic mixture. However, in this context preferably the content of the enantiomer corresponding to that of Compound I is at least 50%, i.e. at least as the racemic mixture, preferably Compound I is in enantiomeric excess.

In the present context for the pharmaceutical uses it is understood that when specifying the enantiomer form of the compound trans-4-(6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine (e.g. as done in formula (I)), then the compound is relatively stereochemically pure as described above, preferably the enantiomeric excess is of at least 80% (80% enantiomeric excess means that the ratio of I to its enantiomer is 90:10 in the mixture in question) at least 90%, at least 96%, or preferably at least 98%. In a preferred embodiment, the diastereomeric excess of Compound I is at least 90% (90% diastereomeric purity means the ratio of Compound I to cis-4-((1S,3S))-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine is 95:5), at least 95%, at least 97%, or at least 98%.

In a preferred embodiment, the present invention relates to a method of treating Schizophreniform Disorder, Schizoaffective Disorder, Delusional Disorder, Brief Psychotic Disorder, Shared Psychotic Disorder or mania in bipolar disorder, comprising administering a therapeutically effective amount of the compound of formula (I) [i.e. 4-((1R,3S)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine] or a salt thereof.

One embodiment of the invention relates to a method of treating positive symptoms of schizophrenia, negative symptoms and depressive symptoms of schizophrenia comprising administering a therapeutically effective amount of the compound trans-4-(6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine or a salt thereof, preferably the compound of formula (I) or a salt thereof, or in a preferred embodiment a succinate or a malonate salt of the compound of formula (I), preferably the hydrogen succinate or the hydrogen malonate salt of the compound of formula (I).

A further embodiment of the invention relates to a method of treating positive symptoms of schizophrenia comprising administering a therapeutically effective amount of the compound trans-4-(6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine or a salt thereof, preferably the compound of formula (I) or a salt thereof, or in a preferred embodiment a succinate or a malonate salt of the compound of formula (I), preferably the hydrogen succinate or the hydrogen malonate salt of the compound of formula (I).

Another embodiment of the invention relates to a method of treating negative symptoms of schizophrenia comprising administering a therapeutically effective amount of the compound trans-4-(6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine or a salt thereof, or preferably the compound of formula (I) or a salt thereof, or in a preferred embodiment a succinate or a malonate salt of the compound of formula (I), preferably the hydrogen succinate or the hydrogen malonate salt of the compound of formula (I).

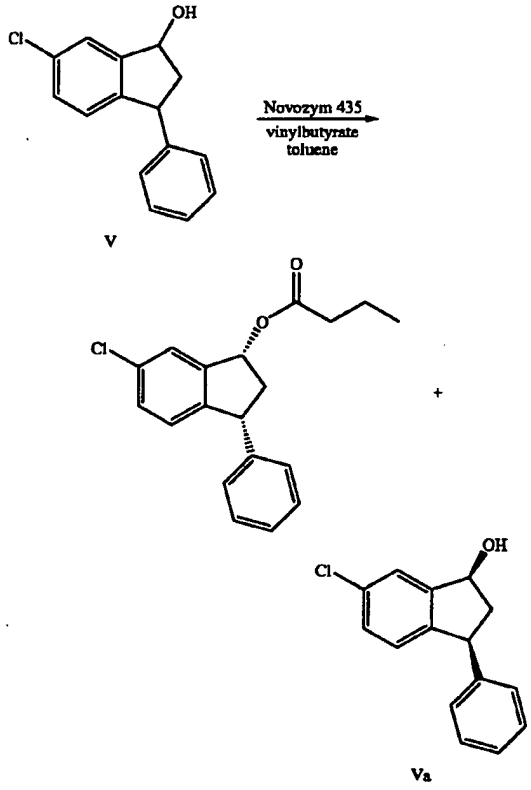
A further embodiment of the invention relates to a method of treating depressive symptoms of schizophrenia comprising administering a therapeutically effective amount of the compound trans-4-(6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine or a salt thereof, preferably the compound of formula (I) or a salt thereof, or in a preferred embodiment the hydrogen succinate or malonate salt of the compound of formula (I).

A further aspect of the invention relates to a method of treating mania and/or maintenance of bipolar disorder comprising administering a therapeutically effective amount of the compound trans-4-(6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine or a salt thereof, preferably the compound of formula (I) or a salt thereof, or in a preferred embodiment a succinate or a malonate salt of the compound of formula (I), preferably the hydrogen succinate or the hydrogen malonate salt of the compound of formula (I).

A further aspect of the invention relates to a method of treating neuroleptic-induced parkinsonism comprising administering a therapeutically effective amount of the compound trans-4-(6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine or a salt thereof, preferably the compound of formula (I) or a salt thereof, or in a preferred embodiment a succinate or a malonate salt of the compound of formula (I),

Example 1b

Synthesis of (1S,3S)-6-chloro-3-phenylindan-1-ol (Va) by Use of Enzymatic Esolution



Compound V (5 g, 20.4 mmol) is dissolved in 150 ml anhydrous toluene. 0.5 g Novozym 435 (Candida Antarctica lipase B) (Novozymes A/S, Fluka Cat.-No. 73940) is added followed by vinylbutyrate (13 ml, 102.2 mmol). The mixture is stirred using mechanical stirrer at 21° C. After 1 day, an additional 0.5 g Novozym 435 is added. After 4 days at a conversion of 54%, the mixture is filtered and concentrated in vacuo to obtain an oil containing a mixture of (1R, 3R)-cis-6-chloro-3-phenylindan-1-ol-butyrate ester and desired compound Va with an enantiomeric excess of 99.2% (99.6% compound Va and 0.4% (1R, 3R)-cis-6-chloro-3-phenylindan-1-ol).

Synthesis of (I) and Removal of the Impurity in form of the cis Diastereoisomer by Precipitation of the Hydrogen Fumarate Salt of (I)

Example 2

Synthesis of (1S,3S)-3,5-dichloro-1-phenylindan (VI, LG=Cl)

Cis-(1S,3S)-6-chloro-3-phenylindan-1-ol (Va) (204 grams) obtained as described in Example 1a is dissolved in THF (1500 ml) and cooled to −5° C. Thionyl chloride (119 grams) is added dropwise as a solution in THF (500 ml) over

a period of 1 h. The mixture is stirred at room temperature over night. Ice (100 g) is added to the reaction mixture. When the ice has melted the water phase (A) and the organic phase (B) are separated, and the organic phase B is washed twice with saturated sodium bicarbonate (200 ml). The sodium bicarbonate phases are combined with water phase A, adjusted to pH 9 with sodium hydroxide (28%), and used to wash the organic phase B once again. The resulting water phase (C) and the organic phase B are separated, and the water phase C is extracted with ethyl acetate. The ethyl acetate phase is combined with the organic phase B, dried with magnesium sulphate, and evaporated to dryness using a rotary evaporator, giving the title compound as an oil. Yield 240 grams, which is used directly in the example 5. Cis/trans ratio 77:23 according to NMR.

Example 3

Synthesis of 3,3-dimethylpiperazin-2-one

Potassium carbonate (390 grams) and ethylene diamine (1001 grams) are stirred with toluene (1.501). A solution of ethyl 2-bromoisobutyrate (500 grams) in toluene (750 ml) is added. The suspension is heated to reflux over night, and filtered. The filter cake is washed with toluene (500 ml). The combined filtrates (volume 4.01) are heated on a water bath and distilled at 0.3 atm. using a Claisen apparatus; first 1200 ml distillate is collected at 35° C. (the temperature in the mixture is 75° C.). More toluene is added (600 ml), and another 1200 ml distillate is collected at 76° C. (the temperature in the mixture is 80° C.). Toluene (750 ml) is added again, and 1100 ml of distillate is collected at 66° C. (temperature in the mixture 71° C.). The mixture is stirred on an ice bath and inoculated, whereby the product precipitates. The product is isolated by filtration, washed with toluene, and dried over night in a vacuum oven at 50° C. Yield 171 g (52%) of 3,3-dimethylpiperazin-2-one. NMR consistent with structure.

Example 4

Synthesis of 2,2-dimethylpiperazine

A mixture of 3,3-dimethylpiperazin-2-one (8.28 kg, 64.6 mol) and tetrahydrofuran (THF) (60 kg) is heated to 50-60° C. giving a slightly unclear solution. THF (50 kg) is stirred under nitrogen, and $LiAlH_4$ (250 g, in a soluble plastic bag, from Chemetall) is added, which gives a slow evolution of gas. After gas evolution has ceased, more $LiAlH_4$ is added (a total of 3.0 kg, 79.1 mol, is used), and the temperature rises from 22° C. to 50° C. because of an exoterm. The solution of 3,3-dimethylpiperazin-2-one is added slowly over 2 hours at 41-59° C. The suspension is stirred for another hour at 59° C. (jacket temperature 60° C.). The mixture is cooled, and water (31) is added over two hours, keeping the temperature below 25° C. (it is necessary to cool with a jacket temperature of 0° C.). Then sodium hydroxide (15%, 3.50 kg) is added over 20 minutes at 23° C., cooling necessary. More water (91) is added over half an hour (cooling necessary), and the mixture is stirred over night under nitrogen. Filter agent Celit (4 kg) is added, and the mixture is filtered. The filter cake is washed with THF (40 kg). The combined filtrates are concentrated in the reactor until the temperature in the reactor is 70° C. (distillation temperature 66° C.) at 800 mbar. The remanence (12.8 kg) is further concentrated on a rotavapor to approximately 10 l. Finally, the mixture is fractionally distilled at atmospheric pressure, and the product is collected at 163-4° C. Yield 5.3 kg (72%). NMR complies with the structure.

Synthesis of (I), Salt Formation of (VII) in Order to Remove cis Diastereoisomer of (VII), and Formation of the Hydrogen Succinate Salt from Crude (I)

Example 10

Synthesis of trans-1-((1R,3S)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazinium (VII) Hydrogen Maleate

Examples 2 and 5 are repeated, giving crude trans-1-((1R,3S)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine (VII) (ca. 20 grams) as an oil, which is further purified by flash chromatography on silicagel (eluent: ethyl acetate/ethanol/triethylamine 90:5:5) followed by evaporation to dryness on a rotary evaporator. Yield 12 grams of the title compound as an oil (cis/trans ratio, 90:10 according to NMR). The oil is dissolved in ethanol (100 ml), and to this solution is added a solution of maleic acid in ethanol to pH 3. The resulting mixture is stirred at room temperature for 16 hours, and the formed precipitate is collected by filtration. The volume of ethanol is reduced and another batch of precipitate is collected.

Yield 3.5 gram solid of the title compound (no cis isomer is detected according to NMR). Melting point 175-178° C.

Example 11

trans-1-((1R,3S)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine (VII)

A mixture of trans-1-((1R,3S)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazinium hydrogen maleate (VII) (9.9 grams), concentrated aqueous ammonia (100 ml), brine (150 ml) and ethyl acetate (250 ml) is stirred at room temperature for 30 min. The phases are separated, and the aqueous phase is extracted with ethyl acetate once more. The combined organic phases are washed with brine, dried over magnesium sulphate, filtered and evaporated to dryness in vacuo. Yield 7.5 grams of oil.

Example 12

Preparation of trans-4-((1R,3S)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine Free Base (I)

Trans-1-((1R,3S)-6-chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine (8.9 grams) (VII) is dissolved in formic acid (10.5 ml) and to the solution is added formaldehyde (10.5 ml). Heated to 60° C. and kept at this temperature for 2½ hours. After cooling of the reaction mixture, water (50 ml) and hexane (50 ml) are added. Adjustment of pH with NaOH (27%, 33 ml) to pH>12. The hexane phase is washed with aq. NaCl (20 ml) and water (20 ml). Hexane is exchanged azeotropic with acetone (90 ml) and the mixture is concentrated. The crude free base in acetone (10 ml) is used without further purification.

Example 13

Trans-4-((1R,3S)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazinium (I) Hydrogen Succinate

Crude trans-4-((1R,3S)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine (I) in acetone solution (10 ml). A suspension of succinic acid (3.4 grams) in acetone (20 ml) is prepared and the trans-4-((1R,3S)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazine (I) solution is added and the mixture is heated to reflux (55° C.). The succinic acid dissolves and during cooling of the solution trans-4-((1R,3S)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazinium (I) hydrogen succinate starts precipitating. Suspension left overnight to precipitate. Trans-4-((1R,3S)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazinium hydrogen succinate is isolated by filtration and washed with acetone (20 ml). The product is dried "in vacuo" at 60° C.

Yield: 7.9 grams.

Differential Scanning Calorimetry shows an endotherm with an onset temperature of 140° C. and a peak at 141° C. corresponding to the alpha form. XRPD diffractogram conforms with the alpha form. $[\alpha]_D^{20}$=22.04° (c=1.0, methanol).

Synthesis of I using 1,2,2-trimethylpiperazine

Example 14

Synthesis of 3,3,4-trimethylpiperazin-2-one

3,3-dimethylpiperazin-2-one (50 grams) is suspended in 1,2-dimethoxyethane (DME) (150 ml) and potassium carbonate (70 grams) is added. Methyl iodide (66.4 grams) is added during half an hour, while the mixture is cooled slightly, allowing the temperature to reach 50° C. The mixture is stirred 9 hours at an oil bath at 40-45° C., and a sample is withdrawn for NMR, which indicates, that there is still 8% starting material left (signal at 2.8 ppm). More methyl iodide is added (4.6 grams), and the mixture is stirred for another 2½ hour at 40° C., and a new NMR sample shows full conversion. The mixture is filtered, and the filter cake is washed with DME. The filtrate is evaporated to dryness giving 41 grams of the title compound. NMR complies with the structure.

Example 15

Synthesis of 1,2,2-trimethylpiperazine

A solution of lithium aluminium hydride in tetrahydrofuran (THF) (1.0 M, Aldrich cat. no. 21,277-6, 90 ml) is heated to 50° C. on an oil batch. Crude 3,3,4-trimethylpiperazin-2-one (10 g) is suspended in THF and is slowly added, giving evolution of gas. The resulting mixture is stirred at 45-56° C. for 4 hours, giving full conversion to the title compound according to NMR (no signal at 1.2 ppm from starting material). The mixture is cooled, and water (3.3 ml) is added, giving evolution of gas. Then a solution of sodium hydroxide in water (15%, 3.3 ml) is added, giving more gas, and finally water (10 ml) is added. The mixture is filtered, and the filter cake is washed with THF (100 ml). The filtrates are concentrated on a rotary evaporator (0.3 atm. and 60° C. in the water batch). The residue is dissolved in THF (200 ml) and dried with sodium sulphate, then the mixture is filtered, and the filtrate is concentrated on a rotary evaporator (0.2 atm and 60° C. in the water batch) giving 6.4 grams of the title compound. NMR complies with the structure, the substance contains some THF.

Example 16

Synthesis of trans-4-((1R,3S)-6-chloro-3-phenylindan-1-yl)-1,2,2-trimethylpiperazinium (I) Hydrogen Fumarate from Compound VI

Cis-(1S,3S)-3,5-dichloro-1-phenylindan (VI with LG=Cl) (17.8 grams) is coupled with distilled 1,2,2-trimethylpipera-

schizophrenia, Schizophreniform Disorder, Schizoaffective Disorder, Delusional Disorder, Brief Psychotic Disorder, Shared Psychotic Disorder and mania in bipolar disorder.

5. The method of claim 4, wherein the disease or disorder is Schizophrenia.

6. The method of claim 5, wherein the schizophrenia comprises positive symptoms, negative symptoms, depressive symptoms, or a combination thereof.

7. The method of claim 4, wherein the disease or disorder is selected from the group consisting of Schizophreniform Disorder, Schizoaffective Disorder, Delusional Disorder, Brief Psychotic Disorder, Shared Psychotic Disorder and mania in bipolar disorder.

8. The crystalline hydrogen succinate salt of claim 1, wherein the salt comprises a beta crystal form characterized by one or more of:

a. an X-Ray powder diffractogram obtained using $CuK_{\alpha 1}$ radiation (λ=1.5406 Å) that has main peaks at the following 2θ-angles: 8.1; 10.5; 11.4; 14.0; 14.6; 15.6; 15.7; 16.2; 17.2; 17.5; 17.9; 18.4; 18.9; 19.2; 20.3; 21.0; 21.9; 22.5; 23.3; and 26.3;

b. an X-Ray powder diffractogram as shown in FIG. 2; and

c. a Differential Scanning Calorimetry (DSC) trace that shows an endotherm with an onset temperature from 135-138° C.

9. The pharmaceutical composition of claim 3, wherein the salt comprises an alpha crystal form characterized by one or more of:

a. an X-Ray powder diffractogram obtained using $CuK_{\alpha 1}$ radiation (λ=1.5406 Å) that has main peaks at the following 2θ-angles: 9.36; 10.23; 11.81; 13.45; 16.21; 16.57; 17.49; 18.89; 19.20; 19.63; 20.01; 20.30; 21.15; 21.53; 21.93; 22.34; 24.37; 25.34; 27.27; and 29.65;

b. an X-Ray powder diffractogram as shown in FIG. 1; and

c. a Differential Scanning Calorimetry (DSC) trace that shows an endotherm with an onset temperature from 139-141° C.

10. The pharmaceutical composition of claim 3, wherein the salt comprises a beta crystal form characterized by one or more of:

a. an X-Ray powder diffractogram obtained using $CuK_{\alpha 1}$ radiation (λ=1.5406 Å) that has main peaks at the following 2θ-angles: 8.1; 10.5; 11.4; 14.0; 14.6; 15.6; 15.7; 16.2; 17.2; 17.5; 17.9; 18.4; 18.9; 19.2; 20.3; 21.0; 21.9; 22.5; 23.3; and 26.3;

b. an X-Ray powder diffractogram as shown in FIG. 2; and

c. a Differential Scanning Calorimetry (DSC) trace that shows an endotherm with an onset temperature from 135-138° C.

11. The method of claim 4, wherein the salt comprises an alpha crystal form characterized by one or more of:

a. an X-Ray powder diffractogram obtained using $CuK_{\alpha 1}$ radiation (λ=1.5406 Å) that has main peaks at the following 2θ-angles: 9.36; 10.23; 11.81; 13.45; 16.21; 16.57; 17.49; 18.89; 19.20; 19.63; 20.01; 20.30; 21.15; 21.53; 21.93; 22.34; 24.37; 25.34; 27.27; and 29.65;

b. an X-Ray powder diffractogram as shown in FIG. 1; and

c. Differential Scanning Calorimetry (DSC) trace that shows an endotherm with an onset temperature from 139-141° C.

12. The method of claim 4, wherein the salt comprises a beta crystal form characterized by one or more of:

a. an X-Ray powder diffractogram obtained using $CuK_{\alpha 1}$ radiation (λ=1.5406 Å) that has main peaks at the following 2θ-angles: 8.1; 10.5; 11.4; 14.0; 14.6; 15.6; 15.7; 16.2; 17.2; 17.5; 17.9; 18.4; 18.9; 19.2; 20.3; 21.0; 21.9; 22.5; 23.3; and 26.3;

b. an X-Ray powder diffractogram as shown in FIG. 2; and

c. a Differential Scanning Calorimetry (DSC) trace that shows an endotherm with an onset temperature from 135-138° C.

* * * * *

EXHIBIT B

(2) Measuring "B Delay" for a National Stage Filing under 35 U.S.C. § 371

For a national stage filing under 35 U.S.C. § 371(b), application pendency must be measured from the date that marks the expiration of 30 months from the priority date of the international application (i.e., not from the date on which the application fulfilled the requirements of 35 U.S.C. § 371). The priority date of the instant patent is August 18, 2003; thus the date that is 30 months from the priority date is Saturday, February 18, 2006. As this date falls on a weekend, the expiration of the 30-month period extends to the following business day, or Tuesday, February 21, 2006 (given the President's Day holiday on Monday, February 20, 2006). Thus, the "actual filing date" for purposes of calculating "B Delay" under 35 U.S.C. § 154(b)(1)(B) and 37 C.F.R. § 1.702(b), is February 21, 2006.[1]

REVIEW OF PATENT TERM ADJUSTMENT CALCULATION

"A Delay"

A first PTO action was due on or before October 14, 2007 (the date that is fourteen months after August 14, 2006, the date on which the application fulfilled the requirements of 35 U.S.C. § 371). See 37 C.F.R. §§ 1.702(a)(1) and 1.703(a)(1). The PTO mailed the first non-final Office Action on May 13, 2008, thereby according a PTO Delay of 212 days. Patentee does not dispute the PTO's calculation for this "A Delay."

In view of the period of "A Delay" detailed above, the total "A Delay" for this patent should be calculated as 212 days.

[1] In contrast to reliance on "the expiration of 30 months from the priority date" for measuring "B Delay," the beginning of the relevant period for purposes of calculating "A Delay" is the date on which an international application fulfills the requirements of 35 U.S.C. § 371. See 35 U.S.C. § 154(b)(1)(A)(i)(II) and 37 C.F.R. § 1.702(a)(1).

Overlap of "A Delay" and "B Delay"

As detailed above, "A Delay" accumulated during the following period:

October 15, 2007, to May 13, 2008.

As detailed above, "B Delay" accumulated during the following period:

February 22, 2009, to July 15, 2009.

As such, the periods of "A Delay" and "B Delay" do not overlap (i.e., occur on the same calendar day).

Applicant Delay

(1) Points of Agreement with PTO Applicant Delay Calculation

(a) Late Reply to Office Action

A reply to an Office Action was due on or before August 13, 2008 (the date that is three months after May 13, 2008, the date on which the Office Action was mailed). Patentee filed a response to the Office Action on November 13, 2008, thereby according an Applicant Delay of 92 days. See 37 C.F.R. § 1.704(b). Patentee does not dispute the PTO's calculation for this Applicant Delay from August 14, 2008 (the day after the date that is three months after the date on which the Office Action was mailed), to November 13, 2008.

(b) Late Reply to Office Action

A reply to an Office Action was due on or before April 22, 2009 (the date that is three months after January 22, 2009, the date on which the Office Action was mailed). Patentee filed a response to the Office Action on July 16, 2009, thereby according an Applicant Delay of 85 days. See 37 C.F.R. § 1.704(b). Patentee does not dispute the PTO's calculation for this Applicant Delay from April 23, 2009 (the day after the date that is three months after the date on which the Office Action was mailed), to July 16, 2009.

all of the papers filed on June 2, 2010 were related to the Request to Correct Inventorship and the Office's response on June 21, 2010 constituted a response to all of the papers filed on June 2, 2010. Furthermore, 37 CFR 1.704(c) explicitly prohibits the Office from double counting periods of Applicant Delay, stating that "[c]ircumstances that constitute a failure of the applicant to engage in reasonable efforts to conclude processing or examination of an application also include the following circumstances, which will result in the following reduction of the period of adjustment set forth in § 1.703 to the extent that the periods are not overlapping" (emphasis added). In the present circumstance, the Office improperly double-counted a single 20 day period (from June 2, 2010 to June 21, 2010) as triggering 40 days of Applicant Delay. In view of the foregoing remarks, Patentee respectfully requests that the period of delay from June 2, 2010 to June 21, 2010 be adjusted to 20 days.

(c) Request to Change Address After Allowance

Patentee filed a Supplemental Application Data Sheet on June 22, 2010, subsequent to the mailing of a Notice of Allowance. The only changes requested on the Supplemental Application Data Sheet were changes to the email address of the practitioner and an inventor's mailing address. Although the filing of a paper to change an address is not mentioned in 37 C.F.R. § 1.704(c)(10), such a filing is specifically addressed in the section of MPEP 2732 that clarifies the types of papers filed after allowance that are not considered to be a failure to engage in reasonable efforts to conclude processing or examination of an application under 37 C.F.R. § 1.704(c)(10). According to MPEP 2732, papers filed after allowance that are "not considered to be a failure to engage in reasonable efforts to conclude processing or examination of an application [include] ... (4) Change of Address" *Id.* Because the Supplemental Application Data Sheet filed on June 22, 2010 related only to changes of address, an assessment of Applicant Delay for this filing is inappropriate. The PAIR/PALM system indicates 43 days of Applicant Delay were accorded in association with this change of address filing. In view of the foregoing remarks, Patentee respectfully submits that 0 days of Applicant Delay should be accorded to the filing.